

**EUROPEAN PATENT APPLICATION**

Application number: 85307531.5

Int. Cl. A61K 31/61

Date of filing: 18.10.85

Date of publication of application:  
13.05.87 Bulletin 87/20

Designated Contracting States:  
AT BE CH DE FR GB IT LI NL SE

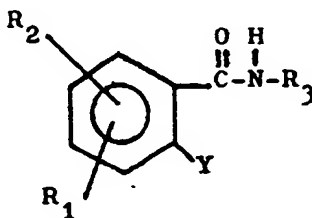
Applicant: UNILEVER PLC  
 Unilever House Blackfriars P.O. Box 68  
 London EC4P 4BQ(GB) GB  
 Applicant: UNILEVER NV  
 Burgemeester s'Jacobplein 1 P.O. Box 760  
 NL-3000 DK Rotterdam(NL)  
 BECHDEFRITLINSEAT

Inventor: Ritchey, Thomas R.  
 208 Somerset Road  
 Norwood New Jersey(US)

Representative: Doucy, Robert Henry et al  
 Unilever PLC Patents Division P.O. Box 68  
 Unilever House  
 London EC4P 4BQ(GB)

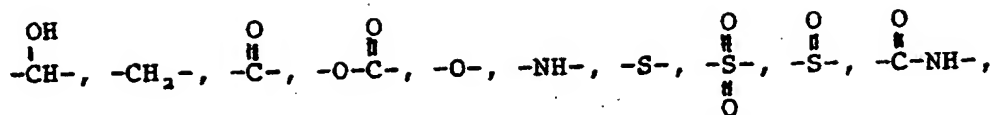
Use of secondary amide compounds for the manufacture of medicaments for the treatment of dermatological inflammation.

The invention concerns the Use of a secondary amide of Formula I for the manufacture of a medicament for the treatment of dermatological inflammation, where Formula I is



EP 0 221 211 A1

where the substituents -R<sub>1</sub> and -R<sub>2</sub> are -H, normal or branched chain or cyclic or fused ring polycyclic or non-fused ring polycyclic alkyl, alkenyl, alkynyl, aryl or heteroaryl groups optionally containing further substituents thereon, said -R<sub>1</sub> and -R<sub>2</sub> substituents comprising up to about 30 carbon atoms when taken together either attached directly to the phenyl ring provided with an amino and a hydroxyl group in an ortho orientation with respect to each other or attached to said phenyl ring through a



$-\text{NH}-\text{CH}_2-$  or  $-\overset{\text{R}}{\text{C}}-\text{NH}-\text{CH}_2-$  group with the proviso that  $-\text{R}_1$  and  $-\text{R}_2$  are not both  $-\text{H}$  and wherein  $-\text{R}_1$  is thiazol-2-yl, benzothiazol-2-yl,  $\text{R}_4$ -substituted phenyl or  $-\text{CH}_2-\text{R}_4$  where  $\text{R}_4$  is  $-\text{CH}_2\text{R}_4$ ,  $-\text{OH}$ ,  $-\text{COOH}$ , the tautomeric pair  $-\overset{\text{CH}_3}{\text{C}}=$  and  $-\overset{\text{CH}_3}{\text{C}}=$ ,  $-\text{CH}_2\text{COOH}$ ,  $-\text{COOCH}_3$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CH}_2\text{COOCH}_3$ ,  $-\text{CH}_2\text{COOC}_2\text{H}_5$ ,  $-\text{NO}_2$  or  $-\text{CX}_1\text{X}_2\text{X}_3$  wherein  $\text{X}_1$ ,  $\text{X}_2$  and  $\text{X}_3$  are halogen atoms,  $-\text{R}_4$  is  $\text{H}$ , alkyl, cycloalkyl, or their unsaturated counterparts, aryl or heteroaryl comprising up to a total of about 24 carbon atoms, and  $-\text{R}_4$  is a  $\text{C}_1$  to  $\text{C}_{24}$  attachment of the same description as  $-\text{R}_1$  and  $-\text{R}_2$ , and  $\text{Y}$  is  $-\text{OH}$  or a phenolic ester group derived from the reaction of such  $-\text{OH}$  group with a carboxylic acid halide or anhydride.

A number of different amido compounds having anti-inflammatory activity have been reported in "Nature", 222, 275:1969; "J. Med. Chem.", 14, 873 (1971); "J. Med. Chem.", 14, 1171 (1971); "J. Med. Chem.", 15, 551 (1972); "J. Med. Chem.", 15, 848 (1972) and in "J. Med. Chem." 16, 493 (1973).

10



20

25

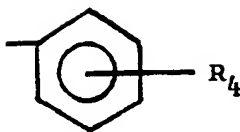
35



40



50

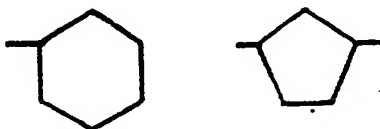


6

wherein  $-R_4$  is selected from the group consisting of  $-\text{CH}_2\text{R}_4$ ,  $-\text{OH}$ ,  $-\text{COOH}$ , the tautomeric pair  $-\text{C}(=\text{O})-\text{CH}_2$  and  $-\text{C}(\text{O})=\text{CH}_2$ ,  $-\text{CH}_2\text{COOH}$ ,  $-\text{COOCH}_3$ ,  $-\text{COOC}_2\text{H}_5$ ,  $-\text{CH}_2\text{COOCH}_3$ ,  $-\text{CH}_2\text{COOC}_2\text{H}_5$ ,  $-\text{NO}_2$ ,  $-\text{CX}_1\text{X}_2$  wherein  $X_1$ ,  $X_2$  and  $X_3$  are halogen atoms, which can all be different halogen atoms or wherein two or more halogen atoms are alike, wherein  $-R_4$  is  $-\text{H}$ , alkyl, cycloalkyl, or their unsaturated counterparts, aryl or heteroaryl comprising up to a total of about 24 carbon atoms, and  $Y$  is  $-\text{OH}$  or a phenolic group derived from the reaction of such  $-\text{OH}$  group with a carboxylic acid halide or anhydride. Alternatively,  $-R_4$  may simply be any aryl or heteroaryl group or  $-\text{CH}_2\text{R}_4$  wherein  $-R_4$  is  $-\text{H}$  or an attachment of up to 24 carbon atoms of the same description as  $-R_1$ , or  $-R_2$  involving the same linking groups between itself and the methylene group directly attached to the amido nitrogen atom.

In the Formula I shown above, alkyl can be straight or branched chain, eg.  $n$ -octyl,  $n$ -decyl or tert-butyl; cycloalkyl can be monocyclic, eg.

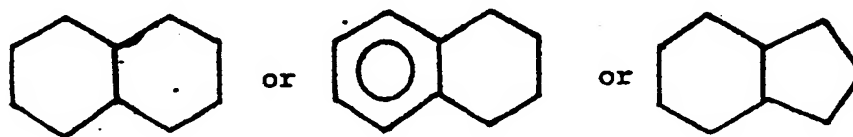
20



26

fused polycyclic, eg.

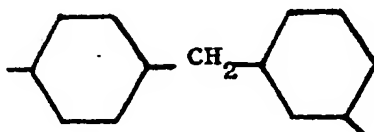
30



35

or non-fused polycyclic, eg.

40



46

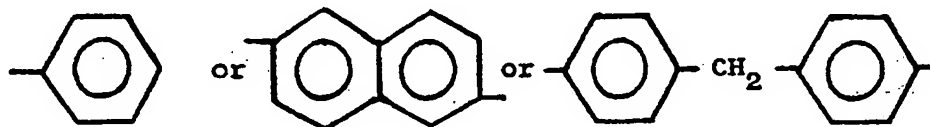
alkenyl can be, eg.  $\text{CH}_2=\text{CH}-(\text{CH}_2)_n$  where  $n$  is an integer or  $\text{CH}_2-(\text{CH}_2)_n\text{CH}=\text{CH}(\text{CH}_2)_m$  where  $n$  and  $m$  are each either zero or an integer it being understood that one or more double bonds may be included in the formula;

alkynyl can be, eg.  $\text{HC}\equiv\text{C}-$  or  $\text{CH}_2(\text{CH}_2)_n\text{C}\equiv\text{C}-(\text{CH}_2)_m$  where  $m$  and  $n$  are each zero or an integer it being understood that one or more triple bonds may be included in the formula;

50

aryl can be mono or polycyclic, eg.

55



and heteroaryl can be mono or polycyclic and can contain 1,2,3 or more heteroatoms, eg. N, O or S, eg.



Each of the respective groups can bear one or more substituents such that  $-R_1$  and  $-R_2$  taken together contain collectively up to about 30 carbon atoms and  $-R_3$  contains up to about 25 carbon atoms.

The medicaments for the treatment of dermatological inflammation may be manufactured by incorporating one or more compounds of Formula I into a pharmaceutically acceptable carrier vehicle which may be petroleum jelly, lanolin, paraffin wax, alkanols and mixtures thereof as well as other comparable vehicles noted in the Examples given below. Alternative vehicles include, ointments, sticks, capsules and tablets, injection solutions or suspensions, other solutions, shampoos, soaps, creams, water, aerosol bases, medicated pads, medicated plasters, medicated bandages, medicated dressings, and medicated catamential and non-catamential tampons. Incorporation of the compounds of Formula I in suitable carriers also results in ear drops, eye drops, nasal drops, anal and vaginal suppositories, enemas and douches as well as liniments, gels and lotions.

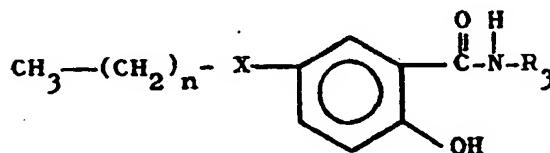
The medicament is placed in intimate contact with the affected organ or is otherwise applied to the affected skin, mucous membrane or organ for a sufficient length of time to relieve inflammation with repeat applications as needed. By making such use of the compounds of Formula I, inflammation in, for example, the ear, eye, nose, mouth, anus and vagina or any other affected organ or cavity is relieved.

Topical application on the skin of the compounds of Formula I in the form eg. of ointments, sticks, shampoos, soaps, creams, water and other solutions, aerosol bases, medicated pads, medicated plasters, medicated bandages, medicated dressings, liniments, gels and lotions results in the relief of skin inflammation. Skin inflammation can be the result of various skin disorders such as eczema, psoriasis, seborrheic dermatitis, contact dermatitis, allergic dermatitis, reactions due to poison ivy, poison oak, stinging nettles, etc. Skin inflammation may also be caused by tissue damage resulting from ultraviolet or other electromagnetic radiation including sunburns, insect and kindred bites and stings as well as thermal burns.

The preferred secondary amides of Formula I bear on the benzene ring at least one lipophilic substituent  $R_1$  and/or  $R_2$  which imparts thereto a distribution coefficient in octanol/water greater than 4.5 and the substituted moieties  $-R_4$  in the phenyl ring of the secondary amido ligand (when the  $-R_3$  ligand takes the form  $-\text{Ph}R_4$ , Ph being a phenyl ring) have a combined overall electron withdrawing effect on said phenyl ring.

The term "distribution coefficient" of a composition as used herein is the  $\log_{10} P$  where P is the ratio of the concentration of the composition in octanol to the concentration of the composition in water in a two phase octanol-water system. A distribution coefficient of, for example, 5 therefore means that the ratio of the concentration of the compound in octanol to the concentration in water is  $10^5$  or 100,000 to 1. The distribution coefficient is a measure of the lipophilic character of the compound. The preferred compounds of Formula I are lipophilic as indicated by a distribution coefficient of greater than about 4.5. The distribution coefficient is however usually less than 10.

The preferred compounds of Formula I are those of the structure shown below:



wherein n is an integer, preferably from 3 to 14,  $R_1$  is as defined above and X is  $-\text{C}(=\text{O})-$  or a covalent bond joining the alkyl group to the phenyl ring. When  $-R_3$  is an  $R_4$ -substituted benzene ring,  $R_4$ -preferably is para  $-\text{NO}_2$ , meta  $-\text{COOC}_2\text{H}_5$  or meta or para  $-\text{CF}_3$ .

Of the preferred compounds, especially preferred are those wherein:

(a) n is 8, X is  $-\text{C}(=\text{O})-$ , and  $-R_3$  is a para-nitrophenyl, (hereinafter called AN-10),

(b) n is 6, X is  $-\text{C}(=\text{O})-$ , and  $-R_3$  is a para-trifluoromethyl-phenyl (hereinafter called APCF3-8).

- (c) n is 8, X is -C(=O)- and -R<sub>1</sub> is a meta-trifluoromethylphenyl (hereinafter called AMCF3-8).  
 (d) n is 5, X is a covalent bond and -R<sub>1</sub> is a para-nitrophenyl (hereinafter called SAN-6).  
 (e) n is 3, X is a covalent bond and -R<sub>1</sub> is a meta-trifluoromethylphenyl (hereinafter called S-4-F).  
 (f) n is 7, X is -C(=O)- and -R<sub>1</sub> is meta-carbethoxyphenyl (hereinafter called ACBXE-9).  
 (g) n is 8, X is -C(=O)- and -R<sub>1</sub> is benzothiazol-2-yl (hereinafter called ABC-4).  
 (h) n is 14, X is -C(=O)-, and -R<sub>1</sub> is thiazol-2-yl (hereinafter called RV-19), and  
 (i) n is 8, X is -C(=O)-, -R<sub>1</sub> is a para-nitrophenyl and the -OH group of Formula I is replaced with a CH<sub>2</sub>=CH-COO-group (hereinafter called acryloyl AN-10).

Very small concentrations of a secondary amide of Formula I in an acceptable carrier vehicle are effective, with concentrations of about 0.1 micrograms per millilitre of carrier vehicle being sufficient in most cases.

In topical applications of a secondary amide of Formula I, a very short contact time of eg. 10 seconds may be sufficient. If necessary, the contact time is extended to about 24 hours. Also, if necessary, such topical application is repeated, as needed.

As stated above, the salicylamides of Formula I are known and described in existing literature. A representative, though not the only available or conceivable method of synthesis thereof is disclosed in EP-A-38191. The following description has been adopted from EP-A-38191. In general such compounds can be prepared by reacting a lower alkyl (R<sub>2</sub>) salicylate ester with an acyl chloride (R<sub>1</sub>COCl) in the presence of a Lewis acid to form an ester of a 5-acylsalicylic acid. The 5-acylsalicylic acid ester is then hydrolysed and the resulting free acid is reacted with a substituted amine or aniline H<sub>2</sub>N-R<sub>3</sub> to form the 5-acylsalicylamide. The term "lower alkyl" as used herein means alkyl of from 1 to 4 carbon atoms. R<sub>2</sub> is n-C<sub>1</sub>, in the case of APCF3-8 and AMCF3-8. It is n-C<sub>2</sub> in the case of AN-10. It is n-C<sub>3</sub>, n-C<sub>4</sub> and n-C<sub>5</sub> in the cases involving ACBXE-9, ABC-4 and RV-19 respectively. In the cases of SAN-6 and S-4-F, the Friedel-Crafts acylation step is replaced by a Friedel-Crafts alkylation process by substituting the acid chloride R<sub>1</sub>-CO-Cl by a normal alkyl halide R<sub>1</sub>Cl. In the case of SAN-6 and S-4-F which are prepared by way of the Friedel-Crafts alkylation initial step, R<sub>1</sub> is C<sub>1</sub> and C<sub>2</sub> respectively. R<sub>3</sub> is a substituted benzene ring or a thiazole or a benzothiazole ring. In the case of a substituted benzene ring, the substituents may be -NO<sub>2</sub> in a para position or -COOC<sub>2</sub>H<sub>5</sub> in a meta position or -CF<sub>3</sub> in either a para or a meta position. When R<sub>3</sub> is one of the two heterocyclic attachments mentioned above, the linking thereof to the secondary amide nitrogen atom occurs through the No.2 carbon atom of the heterocyclic attachment. Acryloyl AN-10 is, as already noted above, an acrylic acid derivative of AN-10 wherein the 2-hydroxy group of AN-10 is replaced by the CH<sub>2</sub>=CH-COO-group. Such replacement is accomplished by the esterification of AN-10 in the manner generally employed for the esterification of phenols. Thus, esterification of AN-10 with acryloyl chloride in pyridine or other base results in the esterified product, ie. acryloyl AN-10.

As a usual procedure, the 5-acyl or 5-alkyl salicylic acid precursor is prepared in a medium or reaction solvent which is customarily considered suitable for conducting a Friedel-Crafts acylation or alkylation with optimal yield, minimal side reactions, non-onerous reaction conditions and minimal reaction time. A preferred reaction solvent is carbon disulfide. Anhydrous aluminium chloride or other Lewis acid is initially added to the carbon disulfide and the mixture is cooled, eg. with ice. A solution of the alkyl salicylate ester, eg. methyl salicylate, and an acyl halide, eg. a chloride (or an alkyl halide as applicable) in carbon disulfide or other reaction solvent is then slowly added and the temperature is maintained below about 10°C. After completion of reaction which may take as long as 24 hours, the reaction mass is poured into ice water and the mixture is then extracted with a suitable solvent such as ether. The ether or other extract is washed with water and then dried over anhydrous sodium sulfate. Thereafter, the ether or other solvent is evaporated in vacuo. The resulting solid residue is dissolved in a suitable solvent such as ethanol and treated with a solution of an alkali metal hydroxide, eg. 2N NaOH solution. After heating to a temperature of between about 80 and 120°C., eg. on a steam bath, the mass is cooled and acidified with a suitable acid such as HCl to a pH of about 1 to precipitate the product. Recrystallisation from ethanol gives purified 5-acylsalicylic acid or 5-alkylsalicylic acid, depending on whether an acid halide or an alkyl halide was the initial Friedel-Crafts reactant.

The 5-acyl or 5-alkyl salicylic acid is reacted with the appropriate substituted aniline or other amine, eg. p-nitroaniline in the case of AN-10, in a suitable reaction solvent such as chlorobenzene. Desirably the 5-acyl or 5-alkylsalicylic acid is pre-reacted with phosphorus trichloride in the solvent at a suitable temperature, eg. between about 55°C and about 80°C. The reaction time is usually between about one and about five hours. The solution is then cooled and the appropriate substituted aniline or heterocyclic amine, eg. p-nitroaniline is then added and the solution is again heated to a suitable temperature, eg. between

about 55°C and about 80°C as previously described for about one to about five hours and is then refluxed until the reaction is complete, eg. for about 24 hours. The solvent is then removed in vacuo and the residue is purified by recrystallisation from a suitable solvent such as a mixture of ethanol and water. The resulting product is an amido compound for use according to the invention.

Detailed descriptions of the methods of synthesis of 5-n-decanoylsalicylic acid and of AN-10 therefrom are given in Examples 1 and 2, respectively, of EP-A-38191.

Example 3 of EP-A-38191 describes toxicity tests for AN-10 performed upon sixteen female white rats of average weight 285 gms. Example 3 concludes with the finding that LD<sub>50</sub> for AN-10 by the single dose oral route is greater than 2000 mg/kg in Osborne-Mendel white rats.

Methods of synthesis of the other preferred compounds of the invention, namely APCF3-8, AMCF3-8, SAN-6, S-4-F, ACBXE-9, ABC-4 and RV-19 follow naturally from the method of synthesis described for AN-10 with appropriate substitution of the respective reactants. See generally, Batista, A J, "Salicylanilides: Design, Synthesis, and In Vitro Evaluation as Inhibitors of Dental Plaque-Forming Microorganisms", PhD. Dissertation, State University of New York at Buffalo, 1980. Acryloyl AN-10 is prepared, as already noted above, from AN-10 by esterification of the phenolic -OH group of AN-10 with acryloyl chloride in pyridine.

Other synthetic routes are described in EP-A-143628 and EP-A-144204.

In the following Examples, percentage amounts are by weight.

#### EXAMPLES 1, 2 & 3 & CONTROL EXAMPLE 4

In a group of 5 male outbred hairless mice, inflammation is induced on their ears by the topical application thereto of 4.0 nmole in acetone solution (total volume 10 microlitre) of the known divalent calcium ionophore (antibiotic A-23187), which is derived from streptomyces chartreusis and is a member of a known class of compounds showing ionophoric activity. See, eg. Pressman, B C, "Biological Applications of Ionophores", Ann Rev Biochem, 45, 501, 1976. Said compound has been found in in vivo tumor promotion studies involving topical application thereof of mice backs to have potent ability to cause skin irritation with white blood cell infiltration, erythema (skin reddening), edema, epidermal hypertrophy and subsequent epidermal hyperplasia. See Marks, F, Furstenberger, G, and Kownatzki, E, "Prostaglandin E-mediated Mitogenic Stimulation of Mouse Epidermis in vivo by divalent cation ionophore A-23187 and by tumor promoter 12-O-tetradecanoyl phorbol-13-acetate, Cancer Res., 41, 696, 1981.

In each animal only one ear is treated, the other untreated ear serving as a control.

Acute inflammation develops on treated mice ears within 4 hours following topical application of A-23187, showing both time and dose dependences. Topical application of steroidal (hydrocortisone) and non-steroidal (indomethacin) anti-inflammatory compositions 30 minutes after application of said ionophore causes reduction of inflammation.

In Examples 1, 2 and 3 the compounds AN-10, APCF3-8 and AMCF3-8, respectively, are topically applied to the treated ears of different groups of five male outbred hairless mice 30 minutes following the topical application thereto of the ionophore A-23187. Specifically, 1.5 micromole of the amido compound in acetone solution (total volume 10 microlitres) is applied topically to treated male outbred hairless mice ears 30 min after topical application thereto of a calcium ionophore (A-23187, 4.0 nmole total volume to 10 microlitre) in acetone. As already noted, in each case, each animal serves as its own control in that only one ear is subjected to said test regime while the other ear is left untouched. Erythema and edema are assessed 4 hours after application of the ionophore. In Control Example 4,

3,4'-5-tribromosalicylanilide (TBS) is applied in the same manner.

TBS is structurally very similar to the compounds of Formula I wherein -R<sub>1</sub> and -R<sub>2</sub> are each -Br and -R<sub>3</sub> is a para-bromo substituted benzene ring.

The varying degrees of effectiveness of AN-10, APCF3-8, AMCF3-8 and TBS in the above-described tests are summarised in Table 1 below.

**TABLE 1**  
**ANTI-INFLAMMATORY ACTIVITY OF SELECTED AMIDO COMPOUNDS**  
**ON INFLAMMATION OF MICE EARS CAUSED BY**  
**CALCIUM IONOPHORE (A-23187)**

	Amido Compounds	Reduction in Edema (%)	Reduction in Erythema (%)
Example 1	AN-10	59	59
Example 2	APCF3-8	48	57
Example 3	AMCF3-8	80	76
Control			
Example 4	TBS	12	35

From the data summarised in Table 1, of the four amido compounds tested for anti-inflammatory activity, only TBS is essentially inactive at the concentration used, whereas AN-10, APCF3-8 and AMCF3-8 are all effective anti-inflammatories. Of the two isomers APCF3-8 and AMCF3-8 (which differ from each other in the position of the -CF<sub>3</sub> group), the meta isomer has a significantly higher level of activity, i.e. the meta isomer shows about 30% more edema reduction activity and about 20% more erythema reduction activity than the para isomer.

This fact is suggestive of a structure/function relationship in the inflammation reduction and/or inhibition process. Along the same lines it may be speculated as a theory underlying the mode of action of the salicylamides of Formula I, that the relative ineffectiveness of TBS is due to the decreased lipophilicity of such compound when alkyl, alkanoyl or similar -R<sub>1</sub> and -R<sub>2</sub> attachments (as already defined above) are substituted by -Br thereby leading to decreased dermal penetration.

#### EXAMPLES 5 TO 11

Acute inflammation is induced by the application of 4 nano mole of the antibiotic A-23187 to the ears of young, male, adult hairless outbred mice (Skh:hr-1 strain). Thereafter, one of the compounds AN-10, AMCF3-8, ACBXE-8, acryloyl AN-10, S-4-F and SAN-6 is applied to the affected ears and the degree of reduction in edema (inflammation) noted.

The method used in the present Examples differs from the method used in the preceding Examples in two respects. Firstly, in the present Examples test animals are assigned to different treatment groups in which each ear of an animal receives the same assigned treatment, i.e. the test animals of the present Examples do not serve as their own controls as they do in the preceding four Examples.

Secondly, in the expression of the data, the objective parameter of ear weights is used as the sole data source (for the reduction of edema) as erythematous responses are not recorded. Ear weights are determined by sacrificing the animals four hours after initial application of the antibiotic A-23187 or other control material by the use of CO<sub>2</sub> gas. Thereafter, the ears are excised by cutting along the characteristic ridge readily discernible along the inner aspect of the ears. Wet and dry ear weights are used to determine the extent of the edema or inflammation present.

In Study A, 28 test animals are randomised into four treatment groups of seven each and subjected to the following ear treatment regimen:

- Group A -A-23187
- Group B -A-23187 + AN-10
- Group C -AN-10
- Group D -Acetone

Each animal is dosed with a treatment consisting of a 10 microlitre quantity of the assigned test material solution (or pure acetone in the case of the animals of Group D) applied to the outer aspect of both ears, i.e. 20 microlitre of test material per ear. The concentrations of the respective materials in acetone solution are such that a 10 microlitre dose of a solution of the antibiotic A-23187 contains 4 nano mole of such antibiotic. The corresponding quantity in the case of the AN-10 in acetone solution is 1.5 micromole. The animals of Groups A and B are initially treated with the acetone solution of A-23187. In the case of the animals in Group B alone, 10 microlitre of the acetone solution of AN-10 is applied to the affected ears 1 hour after the application of the above-mentioned quantity of a solution in acetone of the antibiotic A-23187.



The animals of Group C receive a 10 microlitre dose per ear of the AN-10 in acetone solution alone. The animals of Group D receive a dose of 10 microlitre per ear of pure acetone. All the test subjects are sacrificed four hours after the application of A-23187 to the animals of Groups A and B or the other test materials in the case of the animals of Groups C and D. The results are summarised in Table 2 given below.

A second group of studies (Study B) is conducted on two consecutive days with two sets of mice - (totalling 80 animals) received from the same shipment.

The first batch of 40 animals is divided into 8 groups of 5 each. On Day 1, the six salicylamides AN-10, AMCF3-8, ACBXE-9, acryloyl AN-10, S-4-F and SAN-6 are applied as test solutions to the untreated ears of each group of 5 animals to ascertain whether or not any of the compounds possesses inflammatory potential. The remaining two groups of 5 animals each serve as controls and their ears are dosed with A-23187 and acetone respectively. The respective quantities of the test and control materials and the method of administration is identical with that described for Study A. It is found that none of the six compounds being tested cause any noticeable inflammation.

On Day 2, using the second set of 40 mice, sub-divided into 8 groups of 5 each, the six compounds in question are applied as acetone solutions in the manner described under Study A to mice ears inflamed with A-23187 again, as described in Study A above. As with the studies conducted on Day 1, the remaining two groups of 5 animals each serve as controls and their ears are dosed with A-23187 and acetone respectively.

The amount of each salicylamide compound applied is kept constant, for Days 1 and 2, at 1.5 micromole per 10 microlitre of test solution. Sacrifice begins four hours after application of A-23187, on both days, and the results are recorded. Table 2 summarises the results of the regimen of testing involved with each one of the 30 animals in question on Day 2 with the remaining 10 animals serving as controls as already noted. Table 2 shows the reduction in edema observed with the use of each one of the six salicylamide compounds tested.

TABLE 2

Example (s) 5 and 6	Compound	Reduction in Edema (%)	
		Study A	Study B
	AN-10	55	81
7	Acryloyl AN-10	*	82
8	AMCF3-8	*	81
9	ACBXE-9	*	76
10	S-4-F	*	70
11	SAN-6	*	59

\* not tested

Examination of the above data indicates that all six of the salicylamide compounds tested, AN-10, acryloyl AN-10, AMCF3-8, ACBXE-9, S-4-F and SAN-6 exhibit significant anti-inflammatory activity under the test conditions.

The variation noted in the activity levels for AN-10 are probably the results of individual differences between the 5 animals tested on Day 1 and the 5 animals tested on Day 2 as well as possible non-uniformity of testing conditions on the days in question. It is believed that such differences may be minimised and possibly eliminated by making use of a larger number of animals in each test group and by conducting such tests at the same time and under as uniform conditions as possible.

#### EXAMPLE 12

An ointment is prepared incorporating the compound AN-10 as an active ingredient. The ointment comprises the respective ingredients in the percentages shown below:

	<u>Ingredient</u>	<u>%</u>
5	AN-10	1
	Anhydrous wool fat	2
	Viscous paraffin	10
10	White petroleum jelly	to 100

AN-10 is substituted by an equivalent quantity of any one of the compounds of Formula I, eg. APCF3-8, AMCF3-8, ACBXE-8, acryloyl AN-10, S-4-F and SAN-6 as well as mixtures thereof to form comparable ointments.

The resulting ointment is applied on the skin to relieve an inflammatory condition thereof in sufficient amount to cause the spreading of 0.01 microgram to 500 microgram of the active compound per square centimetre of the dermal area affected.

#### EXAMPLE 13

An ointment of comparable efficacy to that described in Example 12 is made with the following ingredients:

	<u>Ingredient</u>	<u>%</u>
	Compound of Formula I	1
30	Cetyl alcohol	2.4
	Anhydrous wool fat	1
	Viscous paraffin	15
35	White petroleum jelly	to 100

The resulting ointment is applied to the skin to relieve inflammation caused by a painful skin condition in the manner described in Example 12.

#### EXAMPLE 14

The secondary amides may also be used according to the invention for the manufacture of medicaments in a solid form. Such forms have use as a stick-type composition intended for application to the lips or other parts of the body. Such compositions consist essentially of from 0.001% to 10%, preferably 0.01% to 5% of a compound of Formula I, eg. acryloyl AN-10, and from 50% to 98%, preferably 60% to 90% of an emollient. This composition can further consist essentially of from 1% to 20%, preferably 5% to 15%, of a suitable thickening agent, and optionally emulsifiers and water. Thickening agents include without limitation: cross-linked carboxy polymethylene polymers, methylcellulose, gum tragacanth, gum kharaya, xanthan gums and bentonite. Suitable emulsifiers are of a nonionic, anionic or cationic variety. Examples of suitable nonionic emulsifiers include fatty alcohols having 10 to 20 carbon atoms, fatty alcohols having 10 to 20 carbon atoms condensed with 2 to 20 moles of ethylene oxide or propylene oxide, alkyl phenols with 6 to 12 carbon atoms in the alkyl chain condensed with 2 to 20 moles of ethylene oxide, mono- and di-fatty acid esters of ethylene glycol wherein the fatty acid moiety contains from 10 to 20 carbon atoms, fatty acid monoglycerides wherein the fatty acid moiety contains from 10 to 20 carbon atoms, diethylene glycol, glycerol, sorbitol, sorbitan, polyoxyethylene sorbitol, polyoxyethylene sorbitan, and hydrophilic wax esters. Suitable anionic emulsifiers include the fatty acid soaps, eg. sodium potassium and triethanolamine soaps.

wherein the fatty acid moiety contains from 10 to 20 carbon atoms. Other suitable anionic emulsifiers include the alkali metal, ammonium or substituted ammonium alkyl sulfates, alkyl arylsulfonates, and alkyl ethoxy ether sulfonates having 10 to 30 carbon atoms in the alkyl moiety. The alkyl ethoxy ether sulfonates contain from 1 to 50 ethylene oxide units. Satisfactory cationic emulsifiers are the quaternary ammonium, morpholinium and pyridinium compounds. Certain of the emollients noted below also have emulsifying properties.

Suitable emollients include lanolin and its derivatives, namely: lanolin, lanolin oil, lanolin wax, lanolin alcohols, lanolin fatty acids, isopropyl lanolate, ethoxylated lanolin, ethoxylated lanolin alcohols, ethoxylated cholesterol, propoxylated lanolin alcohols, acetylated lanolin acetylated lanolin alcohols, lanolin alcohols linoleate, lanolin alcohols ricinoleate, acetate of lanolin alcohols ricinoleate, acetate of ethoxylated alcohols - esters, hydrogenolysis products of lanolin, ethoxylated hydrogenated lanolin, ethoxylated sorbitol lanolin, and liquid and semi-solid lanolin absorption bases.

Additives commonly found in topical compositions such as preservatives, eg. methyl and ethyl paraben, dyes and perfume are advantageously included in any of the afore-mentioned compositions.

An exemplary solid stick according to this invention containing one or more of the compounds of Formula I is prepared by shaping and molding the following ingredients:

	<u>Ingredients</u>	<u>%</u>
20	APCF3-8	1
	Carnauba wax	40
	Lecithin	40
25	Methyl cellulose	10
	Glycerol	5
	Water	to 100

The resulting solid stick of this Example is applied upon the skin to relieve inflammation in substantially the same manner as with the ointment described in Example 12.

#### EXAMPLE 15

A medicament for the treatment of dermatological inflammation may also be formulated in a solution form. The solution form of the composition consists essentially of from 0.001% to 10%, preferably 0.01% to 5% of a compound of Formula I, eg. ACBXE-9, and the balance being a suitable organic solvent. Suitable organic materials useful as the solvent or a part of a solvent system are as follows: propylene glycol, glycerine, ethanol, sorbitol esters, 1,2,6-hexanetriol, isopropanol, diethyl tartrate, butanediol, and mixtures thereof. Such solvent systems can also contain water.

Accordingly, a solution is prepared as follows:

	<u>Ingredient</u>	<u>%</u>
50	Propylene glycol	10
	Glycerine	27
	ACBXE-9	1
	Ethanol	50
55	Water	to 100

The solution is applied to the affected skin in substantially the same manner as that described for the ointment of Example 12.

#### 5 EXAMPLE 16

The solution of Example 15 is incorporated in a closed metal container fitted with an aerosol cap and pressurised using conventional methods up to 100 psi pressure with butane gas. The resulting aerosol is used as a convenient method of administering an anti-inflammatory composition comprising one or more  
10 compounds of Formula I, eg. ACBXE-9, for the relief of painful skin conditions. The composition of the aerosol is applied to the affected area of the skin at periodic intervals for the relief of inflammation, and preferably every four to twelve hours.

#### 15 EXAMPLE 17

A medicament may also be formulated in a cream form. The creams consist essentially of from 0.001% to 10%, preferably 0.01% to 5% of a compound or compounds of Formula I, eg. S-4-F, from 5% to 50%, preferably 10% to 25% of an emollient, and the balance water. The emollients described above with respect  
20 to the medicaments in a stick form (Example 14) are equally suitable herein. Optionally, the cream form contains a suitable emulsifier. The emulsifiers described in Example 14 above are also equally suitable herein. When an emulsifier is included, it is in the composition at a level from about 2% to about 10%, preferably 5%.

A cream is prepared by mixing together the following ingredients:

25	<u>Ingredient</u>	<u>%</u>
	S-4-F	1
30	Ethoxylated cholesterol	20
	Sorbitol	5
	Water	to 100

35 The resulting cream is applied to the skin to relieve inflammation in the same manner as that described for the ointment of Example 12.

#### 40 EXAMPLE 18

A lotion is prepared incorporating one or more compounds of Formula I, eg. SAN-6 by mixing together the following ingredients in the stated percentages on a wt/wt basis:

45

50

55

	<u>Ingredient</u>	<u>g</u>
	SAN-6	1
6	Viscous paraffin oil	10
	Ethanol	2
	Glycerol	1
	Propylene glycol	2
10	Sorbic acid	0.15
	Mixture of cetylstearyl alcohol and sodium cetylstearylsulfate	0.5
15	and a non-ionic emulsifier	
	Perfume oil of Lily of the Valley	0.1
	Water	to 100

20 In an advantageous alternative embodiment, the above lotion contains 5% of a sun screen, eg. para-  
amino benzoic acid or PABA at the expense of the water ingredient.

The resulting lotion is topically applied to relieve inflammation of the skin in the same manner as that  
described for the cream of Example 17.

#### 25 EXAMPLE 19

One or more compounds of Formula I, eg. AN-10, are formulated into a gel form by simply admixing a  
suitable thickening agent with the above-described solution composition of Example 15. Examples of  
30 suitable thickening agents include: cross-linked carboxy polymethylene copolymers, methyl cellulose, gum  
tragacanth, gum kharaya, xanthan gums and bentonite. The gelled compositions consist essentially of from  
0.001% to 10%, preferably 0.01% to 5% of a compound or compounds of Formula I, from 5% to 75%  
preferably 10% to 50% of an organic solvent, 0.5% to 20%, preferably 1% to 10% of the aforementioned  
thickening agent, the balance being water. Suitable organic solvents include without limitation glycerine,  
35 sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, diethyl tartrate, butanediol, and mixtures thereof.

A gel is prepared by mixing together the following ingredients:

	<u>Ingredient</u>	<u>g</u>
40	AN-10	1
	1,2,6-hexanetriol	45
45	Bentonite	8
	Water	to 100

50 The resulting gel is applied to the skin to relieve inflammation in the same manner as that described for  
the cream of Example 17 noted above.

#### EXAMPLE 20

55 A liniment is prepared from a gel composition of Example 19.

In the aforementioned gel composition, the presence of the bentonite thickening agent is eliminated and  
the balance is made up with 1,2,6-hexanetriol.

The resulting liniment is applied to the skin to relieve inflammation in the same manner as that noted for the gel of Example 19.

#### 5 EXAMPLE 21

One or more compounds of Formula I, such as AMCF3-8 is incorporated in a suppository for intraanal use.

A suppository is prepared by mixing together the following ingredients in the weight ratios shown:

	<u>Ingredients</u>	<u>%</u>
	AMCF3-8	1
15	Cocoa butter	93
	Zinc oxide	3
	Menthol	2
20	Balsam Peru	1

Said suppository is prepared by melting the cocoa butter base at a temperature of about 39°C and adding the remaining ingredients, including AMCF3-8 to the melt, with blending, to provide a homogeneous system. The cocoa butter based resulting melt is poured into moulds of appropriate dimensions and allowed to solidify. The resulting product is a lubricious suppository which melts at body temperature to release the AMCF3-8 or other salicylamide compound to provide improved anti-inflammatory benefits.

Intraanal administration of the resulting suppository is effective in relieving inflammation. The application is repeated as necessary.

#### 30 EXAMPLE 22

A vaginal suppository is made generally following the procedure described above in Example 21 for making an anal suppository. The vaginal suppository has the composition noted below:

	<u>Ingredient</u>	<u>%</u>
	AMCF3-8	1
40	Glycerine	5
	Glyceryl monopalmitate	3
	Glyceryl monostearate	3
45	Hydrogenated palm kernel oil fatty acids	50
	Hydrogenated coconut fatty acids	to 100

In place of AMCF3-8, any one or more the compounds of Formula I may be employed. Intravaginal administration of the resulting suppository is effective in relieving vaginal inflammation. The application is repeated as necessary.

#### 55 EXAMPLE 23

An aqueous preparation containing one or more of the compounds of Formula I, such as acryloyl AN-10 is incorporated in an aqueous composition to form a douche for intravaginal administration. A composition is prepared which contains the following ingredients in the weight percentages shown below:

	<u>Ingredient</u>	<u>%</u>
	Acryloyl AN-10	1
5	Acetic acid	6
	Sodium acetate	6
	Water	to 100

10

Said composition advantageously further incorporates inert but pharmaceutically acceptable colouring matter and fragrances.

The use of the resulting composition as an intravaginal douche results in the alleviation of intravaginal inflammation.

15

#### EXAMPLE 24

One or more compounds of Formula I such as S-4-F is incorporated in a shampoo for application to the scalp.

20

A shampoo is prepared by dissolving one part by weight of S-4-F in 10 parts by weight of ethanol and incorporating the resulting solution in a shampoo base. The shampoo base contains the following ingredients:

25

	<u>Ingredient</u>	<u>%</u>
	Polyoxyethylene sorbitan monostearate	70
	Triethanolamine lauryl sulfate	10
30	Water	20

One part by weight of the S-4-F in ethanol solution is added to nine parts by weight of the above-described shampoo base to form a medicated shampoo.

35

Inflammation of the scalp is effectively alleviated by the use of such shampoo with repeat applications as needed.

#### EXAMPLE 25

40

Medicated ear drops containing one or more of the compounds of Formula I such as AN-10 are prepared by the mixing together of the following ingredients in the parts by weight noted below:

	<u>Ingredient</u>	<u>%</u>
45	AN-10	1
	Triethanolamine polypeptide oleate-condensate	10
	Chlorbutanol	0.5
50	Propylene glycol	to 100

The administration of the resulting ear drops into the ear cavity or auditory canal, with repeated applications as needed, results in the relief of inflammatory conditions of the ear.

55

EXAMPLE 26

Nose drops containing one or more of the compounds of Formula I such as APCF3-8 are prepared by mixing such compound together with the other ingredients in the proportions noted below:

5

	<u>Ingredient</u>	<u>%</u>
	APCF3-8	1
10	Essentail oil of cajeput	0.5
	Essential oil of eucalyptus	0.5
	Essential oil of peppermint	0.5
15	Cottonseed oil	to 100

Administraiton of three to four drops in each nostril of nose drops of the composition noted above three to four times daily results in the relief of inflammation of skin and the nasal mucous membranes.

20

The composition described above may alternatively be incorporated into a compressed air nebulizer and administered in like manner with equal efficacy.

EXAMPLE 27

25

Eye drops containing one or more of the compound of Formula I such as ACBXE-9 are prepared by mixing together the following ingredients in the proportions noted below:

	<u>Ingredient</u>	<u>%</u>
30	ACBXE-9	1
	Ethyl alcohol	0.5
	Thimerosal (preservative)	0.001
35	Propylene glycol	10
	Sodium chloride	3
	Water	to 100

40

The application of one or two drops of eye drops of the above composition, repeated as required, is effective in reducing inflammation.

45 EXAMPLE 28

Medicated sanitary napkins, medicated pads and medicated dressings are prepared by the incorporation of one or more of the compounds of Formula I in a suitable cotton wool or other absorbent article.

A sanitary napkin is prepared in accordance with the method described in Example 3 of US-A-4 226 237.

The resulting sanitary napkin is sprayed with a 10% wt/wt acryloyl AN-10 in acetone solution to ensure a concentration spread of 0.01 gram AN-10 per square centimetre of the napkin. After drying in an aerated chamber at room temperature the napkin is hermetically sealed in a polyethylene or metal foil envelope.

The resulting pad is effective in relieving inflammation when used as a medicated pad.

55



EXAMPLE 29

A pad is prepared in a size other than that to which the teachings of US -A-4 226 237 are confined to thereby produce a medicated pad or a medicated dressing for use in the bandaging of wounds and lacerations. The resulting pads and dressing when made of selected differing dimensions are effective in relieving inflammation when used as medicated pads and as medicated dressings.

EXAMPLE 30

One or more compounds of Formula I, such as acryloyl AN-10 are incorporated in plasters and bandages.

To this purpose, a plaster or a bandage is sprinkled with a 10% wt/wt acryloyl AN-10 in acetone solution to the extent of 0.01 gram acryloyl AN-10 per square centimetre of surface area. Following drying in an aerated chamber at room temperature, the resulting plasters and bandages are stored in hermetically sealed polyethylene or metal foil envelopes to prevent loss of the salicylamide compound from the medicated plaster or medicated bandage.

The term plaster as used herein means a wound dressing which has an adhesive coated on one side thereof. Advantageously, the adhesive material is one which is not affected by the acryloyl AN-10 in acetone solution. The term bandage as used herein means a roll of cotton or other fabric of sterile nature without the incorporation therein of an adhesive which is used in the dressing of wounds.

The acryloyl AN-10 impregnated plaster or bandage is used with enhanced, therapeutic value when utilised in the dressing of wounds by relieving inflammation associated with wounds or lacerations.

EXAMPLE 31

One or more of the compounds of Formula I, such S-4-F are incorporated in a catamenial or non-catamenial tampon.

A catamenial tampon is prepared in accordance with the method described in US-A-4 226 237, of the kind shown in the illustrative embodiments included in Figures 8 and thereof.

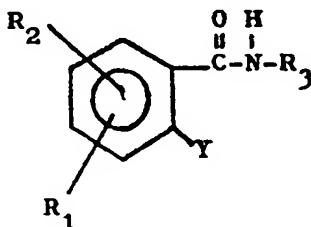
The outer surface of said catamenial tampon is sprinkled with a 10% wt/wt acetone solution of S-4-F in an amount sufficient to provide a concentration of 0.01 gram of such compound per square centimetre of the outer surfaces of such tampon. Following drying in an aerated chamber at room temperature, the tampon is stored in a sealed polyethylene or metal foil pouch, in order to guard against the loss of any S-4-F compound prior to the use of such tampon.

When the resulting catamenial tampon is intravaginally worn, relief of intravaginal inflammation is noticed.

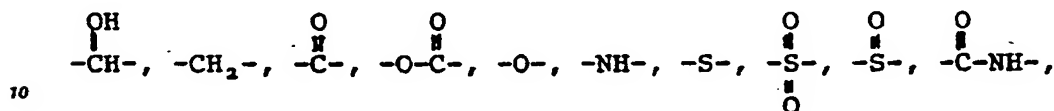
When said tampon is prepared in appropriate (smaller) dimensions, such as to enable the same to fit snugly within other body cavities such as the ears and the nose without causing any discomfort to the wearer, similar relief from inflammation of skin as well as affected mucous membranes is noticed.

Claims

1. Use of a secondary amide of Formula I for the manufacture of a medicament for the treatment of dermatological inflammation, where Formula I is



where the substituents  $-R_1$  and  $-R_2$  are  $-H$ , normal or branched chain or cyclic or fused ring polycyclic or non-fused ring polycyclic alkyl, alkenyl, alkynyl, aryl or heteroaryl groups optionally containing further substituents thereon, said  $-R_1$  and  $-R_2$  substituents comprising up to about 30 carbon atoms when taken together either attached directly to the phenyl ring provided with an amino and a hydroxyl group in an ortho orientation with respect to each other or attached to said phenyl ring through a



15  $-NH-CH_2-$  or  $-C(=O)-NH-CH_2-$  group with the proviso that  $-R_1$  and  $-R_2$  are not both  $-H$  and wherein  $-R_2$  is thiazol-2-yl, benzothiazol-2-yl,  $R_4$ -substituted phenyl or  $-CH_2R_4$  where  $R_4$  is  $-CH_2R_4$ ,  $-OH$ ,  $-COOH$ , the tautomeric pair  $-C(=O)CH_2-$  and  $-CH=C(=O)-$ ,  $-CH_2COOH$ ,  $-COOCH_3$ ,  $-COOC_2H_5$ ,  $-CH_2COOCH_3$ ,  $-CH_2COOC_2H_5$ ,  $-NO_2$ , or  $-CX_1X_2X_3$  wherein  $X_1$ ,  $X_2$  and  $X_3$  are halogen atoms,  $-R_3$  is  $H$ , alkyl, cycloalkyl, or their unsaturated counterparts, aryl or heteroaryl comprising up to a total of about 24 carbon atoms, and  $-R_4$  is a  $C_{1-20}$  attachment of the same description as  $-R_1$  and  $-R_2$ , and  $Y$  is  $-OH$  or a phenolic ester group derived from the reaction of such  $-OH$  group with a carboxylic acid halide or anhydride.

20 2. Use of a secondary amide as claimed in Claim 1, wherein in Formula I  $-R_2$  is  $R_4$ -substituted phenyl and  $R_4$  is  $-CX_1X_2X_3$  where  $X_1$ ,  $X_2$  and  $X_3$  are identical halogen atoms.

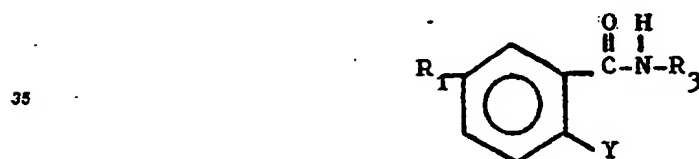
3. Use of a secondary amide as claimed in Claim 2, wherein  $X_1$ ,  $X_2$  and  $X_3$  are fluorine atoms.

25 4. Use of a secondary amide as claimed in Claim 1, wherein in Formula I  $-R_2$  is  $R_4$ -substituted phenyl and  $R_4$  is  $-NO_2$ .

5. Use of a secondary amide as claimed in Claim 1, wherein in Formula I  $-R_2$  is  $R_4$ -substituted phenyl and  $R_4$  is meta- $CF_3$ .

6. Use of a secondary amide as claimed in Claim 1, wherein in Formula I  $-R_2$  is  $R_4$ -substituted phenyl and  $R_4$  is in the para position.

30 7. Use of a secondary amide as claimed in Claim 1, wherein the secondary amide has the formula



40 wherein

- (a)  $R_1$  is n-decanoyl,  $Y$  is hydroxy and  $R_3$  is p-nitrophenyl; or
- (b)  $R_1$  is n-octanoyl,  $Y$  is hydroxy and  $R_3$  is p-trifluoromethylphenyl; or
- (c)  $R_1$  is n-octanoyl,  $Y$  is hydroxy and  $R_3$  is m-trifluoromethylphenyl; or
- (d)  $R_1$  is n-hexyl,  $Y$  is hydroxy and  $R_3$  is p-nitrophenyl; or
- 45 (e)  $R_1$  is n-butyl,  $Y$  is hydroxy and  $R_3$  is m-trifluoromethylphenyl; or
- (f)  $R_1$  is n-nonanoyl,  $Y$  is hydroxy and  $R_3$  is m-carbethoxyphenyl; or
- (g)  $R_1$  is n-decanoyl,  $Y$  is hydroxy and  $R_3$  is benzothiazol-2-yl; or
- (h)  $R_1$  is n-hexadecanoyl,  $Y$  is hydroxy and  $R_3$  is thiazol-2-yl; or
- (i)  $R_1$  is n-decanoyl,  $Y$  is acryloyloxy and  $R_3$  is p-nitrophenyl;

50 or is a mixture thereof.



European Patent  
Office

# EUROPEAN SEARCH REPORT

Application number

EP 85 30 7531

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y,D	EP-A-0 038 191 (RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK) * Pages 11,12; claims *	1-7	A 61 K 31/61
Y	EP-A-0 038 192 (RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK) * Page 4; claims *	1-7	
Y	DE-A-2 755 224 (PROCTER & GAMBLE) * Claims; pages 6-8 *	1-7	
Y	EP-A-0 154 907 (BAYER) * Page 9, lines 14,15; page 10, line 1 *	1-7	
Y	CH-A- 506 292 (MÜHLEMANN) * Page 1, column 2, lines 23-26 *	1-7	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K 31/00
Y	DE-A-1 801 299 (MERCK) * Page 2; claims *	1-7	
Y	FR-A-2 035 771 (ARIES) * Page 1; lines 4-40 *	1-7	
Y	US-A-4 032 635 (UMEZAWA et al.) * Column 1, lines 50-65; column 2, lines 1-57 *	1-7	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 10-06-1986	Examiner THEUNS H.G.
<b>CATEGORY OF CITED DOCUMENTS</b>			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		I : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document	



European Patent  
Office

# EUROPEAN SEARCH REPORT

Application number

EP 85 30 7531

Page 2

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 24, 1981, pages 1245-1249, American Chemical Society, US; R.A. COBURN et al.: "Potential salicylamide antiplaque agents: in vitro antibacterial activity against Actinomyces viscosus" * Whole article *	1-7	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 10-06-1986	Examiner THEUNS H.G.
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document</p>			

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**